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Increased Radiosensitivity in a Child With T-Cell Non-Hodgkin's Lymphoma

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INTRODUCTION

Simon P. Attard-Montalto, MD (Lecturer in Paediatric Oncology)

Radiotherapy is based on the understanding that rapidly dividing malignant cells are radiosensitive. Fractionation, shielding, and focusing of the beam are employed to decrease the toxicity to surrounding tissues which are also radiosensitive. In spite of these precautions, many children suffer from acute, local reactions to radiotherapy such as alopecia, desquamation, and erythema of the skin. Children with ataxia telangiectasia (A-T) are particularly sensitive to radiation [1–4]. This is true for both A-T homozygotes and heterozygotes. Another group of patients have the phenotypic features of A-T but develop ataxia at a later date. These A-T variants also demonstrate abnormal radiosensitivity, albeit to a lesser degree than those patients with classical A-T [2,5,6]. Homozygotes, heterozygotes, and variant forms of A-T have an increased risk of malignant disease [7–12]. Anecdotal reports have described a further group of patients who are phenotypically normal without ataxia, but still develop severe, adverse reactions following exposure to therapeutic irradiation for malignant disease [13,14]. Radiobiological tests in these patients show a spectrum of abnormality, with a variable exaggerated cellular radiosensitivity which is generally less severe than that seen in A-T. In this heterogenous group, unlike those with A-T homozygotes, heterozygotes, and variants, the pattern of malignancy is as yet unknown. We report such a case in a boy with T-cell non-Hodgkin's lymphoma who, despite a normal phenotypic appearance, suffered significant complications following craniospinal irradiation.

CASE HISTORY

Dr. Attard-Montalto. A 7-year-old phenotypically normal Turkish boy presented with a 4 week history of hoarseness, neck swelling, and night sweats. A detailed physical examination revealed generalised lymphadenopathy with involvement of Waldeyer's ring and moderate hepatomegaly.

The haemoglobin was 10 g/dl, total white cell count 9×10^9/l, and platelet count 89×10^9/l. An x-ray of the chest showed a widened mediastinum. Computerised tomography (CT) scanning showed extensive enlargement of the mediastinal and abdominal lymph glands, with deposits in the right kidney. The cerebrospinal fluid (csf) was normal. A bone marrow aspirate showed an abnormal infiltrate constituting 30% of the total cell population. Immunophenotyping showed CD2, CD7, and CD8 positivity, and histology confirmed an immature, lymphoblastic T-cell non-Hodgkin's lymphoma (NHL). Tumour cell karyotyping showed the translocation t(1:14)(p34: q11.2). The serum immunoglobulins were reduced: IgG 3.2 g/l (normal range 6.5–18 g/l), IgA 0.21 g/l (normal 0.6–2.2 g/l) and IgM <0.1 g/l (normal 0.4–2.0 g/l).

Dr. Kingston, in view of these results what treatment did he receive?

Judith Kingston, FRCP (Consultant in Paediatric Oncology)

Treatment was commenced according to the United Kingdom Childrens' Cancer Study Group protocol for

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disseminated T-cell lymphoma [15]. He received an induction schedule over a period of 4 weeks, followed by an early intensification module (week 5), three courses of high dose intravenous methotrexate and a late intensification module (week 20). Clinical and haematological remission was achieved by day 28 of treatment. He tolerated the intensive, early part of treatment without untoward sequelae. After 11 months on maintenance chemotherapy he complained of headache, double vision, and vomiting and was found to have blast cells in the cerebrospinal fluid. A bone marrow aspirate was normal. Treatment was recommenced with high dose dexamethasone and chemotherapy according to a relapse protocol [16]. This included two courses of methotrexate, 12.5 mg intrathecally; high dose systemic cytarabine, 1 g/m^2 intravenously (i.v.) 12 hourly for 5 days, and etoposide, 100 mg/m^2 i.v. daily for 5 days. Following the second course he developed febrile neutropenia and, during the subsequent hospital admission, was noted to have poor coordination, a tremor, and an ataxic gait. These symptoms lasted for a period of 2 days during which time an electroencephalograph showed no abnormality.

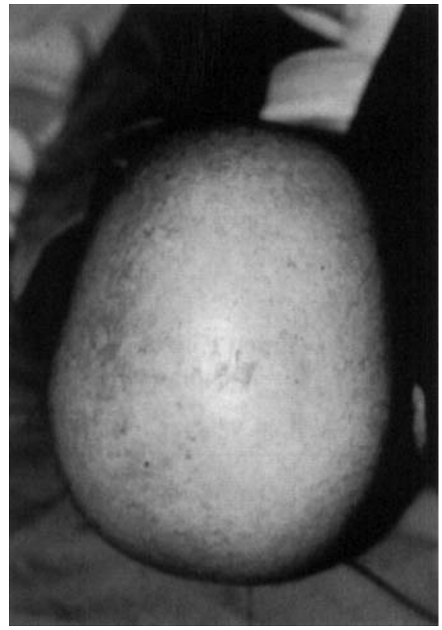

Fig. 1. Scalp showing scarring and patchy pigmentation following radiotherapy.

RADIOTHERAPY

In view of the brevity of these symptoms and normal CT scan, he continued treatment and was referred to Dr. Plowman for craniospinal radiotherapy in accordance with the protocol. Dr. Plowman, what prescription did he receive and were there any problems during radiotherapy?

Nicholas Plowman, FRCP (Consultant Radiotherapist)

Three months after the relapse he received 1,200cGy to the spine in 8 fractions and 2,400cGy to the cranium in 15 fractions over 21 days, by a standard 6MV x-ray technique. This was complicated by nausea, vomiting, a low-grade temperature and profound lethargy. After 2 weeks of treatment he developed severe mucositis and oesophagitis resulting in profound anorexia and a loss of 3.25 kg in weight, equivalent to 14% of his immediate pre-radiotherapy weight. Three weeks after the completion of radiotherapy he developed itching, increased sensitivity and erythema of the skin involved in the radiotherapy field, which rapidly progressed to generalised moist desquamation. The radiation reaction healed after 2 weeks, leaving large areas of depigmentation with patchy scarring and irregular hyperpigmentation over the entire scalp, neck, central thorax, and abdomen (Figs. 1, 2). Radiation-related somnolence developed 4 weeks after radiotherapy and persisted for 3 weeks, compounding the severe anorexia and necessitating the need for total parenteral nutrition (TPN).

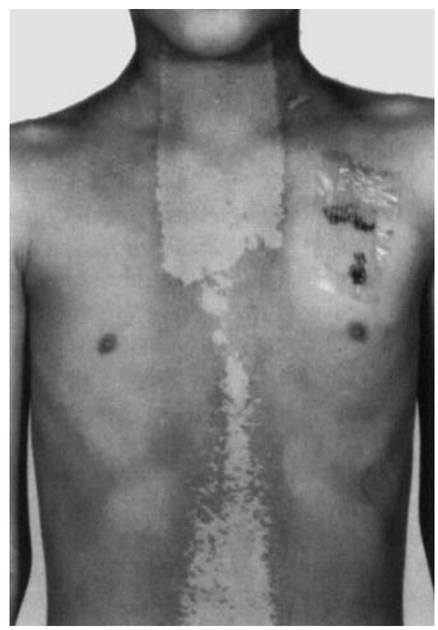

Fig. 2. Chest wall showing large area of depigmentation and scarring in radiotherapy field.

RADIOBIOLOGY

In view of the major complications suffered during radiotherapy, the possibility of an abnormal radiosensitivity was considered. Radiation sensitivity tests were performed on fibroblasts cultured from a skin biopsy taken from the scalp after the acute inflammation had healed. Dr. Arlett, what did these tests entail and how did the results compare with those of normal and radiosensitive individuals?

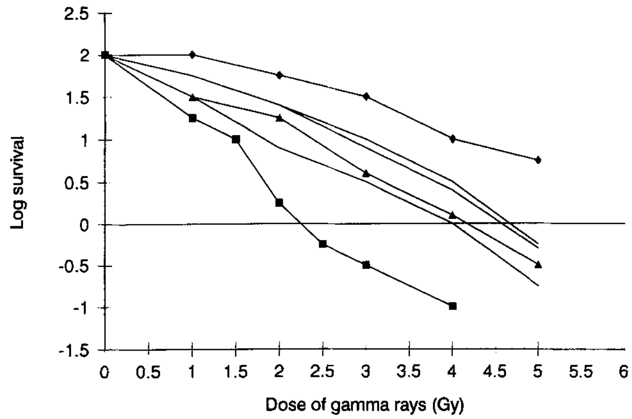

Fig. 3. Cell survival with increasing doses of ionising radiation. —▲—, patient; —◆—, normal; —■—, A-T; —, A-T variants.

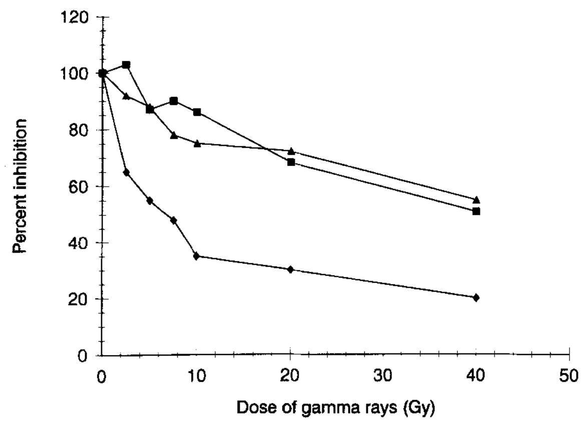

Fig. 4. Inhibition of DNA synthesis with ionising radiation. —▲—, patient (290BR); —◆—, normal (1BR.3); —■—, A-T (AT5BI).

Colin Arlett, PhD (MRC Cell Mutation Unit)

We assessed radiosensitivity by exposing cells from the fibroblast culture (designated 290BR) to ^{60}CO gamma irradiation. The percentage of cells surviving increasing doses of radiation was decreased when compared with normal controls. However, the extent of cell death was less severe than that found in patients with A-T (Fig. 3). The inhibition of DNA synthesis for a given dose of gamma irradiation was also considerably less in these cells when compared with normal controls (142BR and 1BR.3), and similar to the percentage inhibition seen in cells from a patient with classical A-T (AT5BI) (Fig. 4). On the basis of the moderate cellular radiosensitivity and the A-T-like response with respect to radiation resistant DNA synthesis, this patient might well be classified as an A-T variant were it not for the absence of any clinical symptoms of the disease.

The degree of radiosensitivity was also assessed on normal blood lymphocytes. Dr. Taylor, what did these experiments show?

Malcolm Taylor, PhD (Reader in Cancer Studies)

Following exposure of his lymphocytes at G2 (4 hours before harvest), to x-ray doses of 50 and 100cGy, a definite increased level of induced chromosome damage was observed compared with normal. The level of induced chromosome damage overlapped the range of damage seen in irradiated lymphocytes from bona fide A-T patients, although at the lower end of this range. The level of induced damage, however, was higher than the mean level observed in a subgroup of bona fide United Kingdom A-T patients with levels of induced damage intermediate between normal and typical A-T.

We were not able to find sufficient mitoses from the untreated sample to undertake G-banding.

We analysed the haplotypes of the patient and his parents on chromosome 11q22-23 in the region of the A-T gene. Not surprisingly, neither of the patient's haplotypes matched the haplotyped associated, in the UK A-T patients, with later onset ataxia and associated with a smaller increase in cellular radiosensitivity.

Our patient was in remission 6 months after radiotherapy, but almost total alopecia of the scalp persisted. This complication following radiotherapy is unusual but, Dr. Plowman, we believe you have encountered a similar problem previously?

Dr. Plowman. We reported a similar case of a 13-year-old Turkish boy with a T-cell acute lymphoblastic leukaemia (ALL) and a presenting white cell count of 35×10^9/l, who also developed major treatment-related complications in 1990 [13]. This patient had no signs of A-T but developed severe anorexia, 14% loss of body weight, hypertension, congestive heart failure, convulsions, and profound myelosuppression following induction chemotherapy which was identical to the treatment received by the subject of this report [15]. He proceeded to cranial radiotherapy and received 1,800cGy in 10 fractions over 12 days through parallel opposed lateral 6MV x-ray portals. He developed marked erythema and moist desquamation over the scalp which healed by scarring after 18 days. Thirty-three days after radiotherapy, he developed profound tiredness and lethargy which lasted for a period of 3 weeks. His management was further complicated by recurrent otitis media leading to bilateral mastoiditis and deafness. Severe anorexia and myelosuppression persisted for 6 months after radiotherapy and, 10 months after the initial diagnosis, he developed a progressive encephalopathy (attributed to the radiotherapy) and died.

This second patient had major complications following radiotherapy but, in addition, also suffered profound and prolonged myelosuppression after chemotherapy. He had radiobiological tests on fibroblasts obtained from a forearm skin biopsy. Professor Bridges, how did these results differ from those from our patient?

TABLE I. Differences Between 290BR, 180BR, A-T, and A-T Variants

	290BR	180BR	A-T heterozygote	A-T variant	A-T
Ataxia	−	−	−	+	+
Telangiectasia	−	−	−	+	+
Cell killing	++	+++	±[b]	++	+++
Radiation-resistant DNA synthesis	+++	−	−	+++	+++
Radiation-induced clastogenicity	++	ND[a]	±[c]	+	+++

[a]Nd = not done.
[b]Reported to overlap the normal range (Kidson et al., 1982 [31]).
[c]Probably only detectable at G_2 (Scott et al., 1994 [32]).
290BR Current patient fibroblasts.
180BR Previous patient fibroblasts.

Bayn Bridges, PhD (Director, MRC Cell Mutation Unit)

The sensitivity to ^{60}CO gamma irradiation of cells from the fibroblast culture (designated 180BR), established from the latter patient was tested using either dividing cells or cells taken out of cycle (G_0). One hundred and eightyBR fibroblasts showed radiosensitivity indistinguishable from that of fibroblasts from a patient with A-T (AT3BR) and much greater than from normal fibroblasts (154BR and 1BR.3). However, in contrast to cells from a reference patient with S-T (AT4BI), and from the patient under investigation (290BR), 180BR cells showed normal inhibition of DNA synthesis after irradiation.

DISCUSSION

Dr. Attard-Montalto, Vaskar Saha, MD (Senior Registrar), Dr. Bridges, and Osborn Eden, FRCP (Professor of Paediatric Oncology)

Ataxia telangiectasia (A-T) is a rare autosomal recessive condition characterised by the typical physical stigmata of dilated scleral blood vessels and progressive cerebellar degeneration [17], a raised alpha feto-protein level [18], immunodeficiency, a small thymus [7–9], and a characteristic in vitro cell response to gamma irradiation [1–4]. Heterozygotes lack the phenotypic features of A-T, but cultured cells from these patients have an increased sensitivity to ionising radiation [2], though to a lesser degree than cells from homozygotes [1–4]. However, variation in the expression of A-T features is well recognised, suggesting variant expression of the abnormal gene(s), located on chromosome 11 [19]. Those with the A-T variant have raised alpha fetoprotein levels and immunodeficiency but tend to develop signs of cerebellar degeneration after the age of 6 years. The subject of this report developed transient ataxia during an episode of febrile neutropenia but, in view of his otherwise normal neurology and the absence of telangiectasia, it was assumed that the ataxia was related to the fever. There was no increase in the serum alpha fetoprotein in this patient although he did have low serum immunoglobulin levels. The adolescent child reported previously [13] was also phenotypically normal without ataxia but, in this patient, both alpha fetoprotein and immunoglobulin levels were normal.

At the chromosomal level, patients with A-T show two important features which, in the presence of clinical features of cerebellar degeneration, are diagnostic for the disorder. These are, firstly, a large increase in chromosomal radiosensitivity [24–26] and, secondly, an increased level of translocations in peripheral lymphocytes, involving mostly chromosome 7 and 14 [27,28]. We were unable to check for these translocations in somatic cells in the subject of this report who did, however, have an increased chromosomal radiosensitivity. As shown in Table I, in vitro analysis of cell survival, inhibition of DNA synthesis, and radiation-induced clastogenicity in the study patient suggest that he was similar to an A-T variant, rather than a classical A-T or heterozygote [29–32]. However, the absence of phenotypic features and normal alpha fetoprotein argue against this diagnosis. The classical characteristics were also absent in the previously reported adolescent [13].

Other patients with increased cellular radiosensitivity include those with the Nijmegen Breakage Syndrome [33]. However, there was no evidence, in this patient, for the microcephaly and "bird-like" facies of Nijmegen Breakage Syndrome.

Patients with A-T are homozygous for the mutant gene and have an increased risk of developing malignant disease [7–10]. Approximately 30% of patients with A-T may develop a tumour and 80% of these neoplasms are of lympho-reticular cell origin, usually T-cell lineage prolymphocytic leukaemia and non-Hodgkin's lymphoma. They are associated with an increased incidence of high risk features and have a poor prognosis [8,11,20]. The remaining 20% include solid tumours of the oral cavity, breast, stomach, and pancreas [10,21]. Heterozygotes for the mutant gene (A-TH) also have an increased risk of cancer, the most notable being an increase in breast cancer in female carriers [12,22]. This suggests that A-T is an autosomal co-recessive condition [23].

It is difficult to suggest that either of the two children fall into any of the three A-T categories. Taking all the findings together, these two cases suggest that there is an additional group of individuals who lack the phenotypic features of A-T, are also radiosensitive but to a lesser degree than bona fide A-T and who, nevertheless, share the potential for developing malignant lymphoma.

The sensitivity of A-T cells to ionising radiation [1–4] and chemotherapeutic agents [34,35] is linked to a defect in the DNA repair process [23]. While the exact mechanism is unclear, it is possible that at least some of these patients may have a defective topoisomerase II enzyme (which is normally responsible for repairing breakages in double stranded DNA). Therefore, in addition to an increased sensitivity to irradiation, such patients could also develop marked toxicity when treated with topoisomerase II inhibitors such as the anthracyclines and epipodophyllotoxins [36,37]. Indeed, the adolescent child developed severe complications and the subject of this report developed occult toxicity following chemotherapy including etoposide (VP16). This chemosensitivity makes the treatment of lymphoma and leukaemia in these patients hazardous since most current protocols for T-cell disease incorporate both these groups of drugs. These children may suffer fewer complications when treated with "older" leukaemia regimens such as UKALL VIII [38], where the use of topoisomerase II inhibitors is avoided. Cranio-spinal irradiation is contraindicated and can be replaced with courses of high-dose methotrexate given intravenously along with intrathecal methotrexate, which do not appear to produce adverse reactions in patients with A-T.

For many radiosensitive individuals, cell sensitivity tests would show some abnormality and, therefore, highlight the risks of proceeding with radiotherapy and chemotherapy. However, in those patients without physical stigmata, these tests are not performed prior to treatment; the diagnosis is only made retrospectively, after the development of serious chemotherapy or radiotherapy-related complications. Preemptive radiobiological investigation would be helpful in those patients with neurocutaneous manifestations, ataxia, hypogammaglobulinaemia, and in all those with severe, unexpected complications following chemotherapy prior to commencing radiotherapy. Unfortunately, such tests are currently difficult and slow to perform and would result in an unacceptable delay to the therapeutic process. Nevertheless, all patients who demonstrate clinical or cellular radiosensitivity should have appropriate lymphocyte and fibroblast cell cultures established. Only with this data base would it be possible to eventually understand and classify the different radiosensitivity syndromes. Furthermore, in view of the likely increased risk of secondary malignancies developing in these patients with a genetic predisposition, this information would be useful in prognostication for the individual patient and with regards to genetic counselling for their families.

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